

New Zealand Data Sheet

1 PRODUCT NAME

LEVOTHYROXINE 50 microgram and 100 microgram tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Levothyroxine sodium (anhydrous) 50 microgram and 100 microgram.

Each tablet contains 50 micrograms (0.05 mg) or 100 micrograms (0.1 mg) anhydrous levothyroxine sodium, which is the monosodium salt of the levorotary isomer of thyroxine.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Levothyroxine 50 microgram (0.05 mg) tablets are white, uncoated, biconvex tablets, engraved on one face with “LT” and “50” on the other.

Levothyroxine 100 microgram (0.1 mg) tablets are white, uncoated, biconvex tablets, engraved on one face with “LT” and “100” on the other.

The tablets must be swallowed whole. Do not halve the tablets. Dose equivalence when the tablet is divided has not been established.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Levothyroxine is indicated for the treatment of hypothyroidism.

This product should only be prescribed to patients already taking this product who are known to be intolerant to all other levothyroxine containing products.

This product may also be prescribed to patients already taking this product who are not known to be intolerant to all other levothyroxine containing products, but for whom changing to another levothyroxine containing product is not clinically appropriate.

4.2 Dose and method of administration

Thyroxine has a narrow therapeutic index. Appropriate thyroxine dosage is based upon clinical assessment and laboratory monitoring of thyroid function tests. During the initial titration period, careful dosage titration and monitoring is necessary to avoid the consequences of under- or over-treatment. The symptoms of excessive thyroxine dosage are the same as many features of endogenous thyrotoxicosis.

A pre-therapy ECG is valuable, as changes induced by hypothyroidism may be confused with ECG evidence of ischaemia. If the increase in metabolism is too rapid (causing diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischaemia), dosage must be reduced or withheld for a day or two, then restarted at a lower level.

In younger patients, and in the absence of heart disease, a serum levothyroxine (T4) level of about 70 to 160 nanomols per litre, or a serum thyrotrophin level of less than 5 milliunits per litre, should be aimed at. In those aged over 50, and/or in the presence of heart disease, clinical response is probably a more acceptable criterion of dosage than serum levels.

In patients whose medications include levothyroxine and known interfering agents, administration should be separated by at least 4 hours (see Section 4.5 Interactions with other medicines and other forms of interactions).

Dose

Adults

Initially 50 to 100 micrograms daily and adjust at 4 to 6 week intervals by 50 micrograms until normal metabolism is steadily maintained. This may require doses of 100 to 200 micrograms daily.

Patients over 50 years, elderly, or with diabetes or cardiac symptoms

With patients aged over 50 years, it is not advisable to exceed 50 micrograms a day initially. Where there is cardiac disease 25 micrograms, given as 50 micrograms on alternate days, is more suitable. In this condition the daily dosage may be slowly increased by 25 micrograms increments (given as 50 micrograms on alternate days) at intervals of perhaps four weeks. This dosing regimen is illustrated in **Table 1** below.

Table 1 – Recommended dosage regimen for levothyroxine tablets

DAILY DOSE	DOSING REGIMEN
25 micrograms	One 50 microgram tablet on alternate days
50 micrograms	One 50 microgram tablet daily
75 micrograms	One 50 microgram tablet daily and one 50 microgram tablet on alternate days
100 micrograms	One 100 microgram tablet daily
125 micrograms	One 100 microgram tablet daily and one 50 microgram tablet on alternate days

The initial dose and any dose increments should be carefully chosen in elderly and in patients with cardiac symptoms, diabetes mellitus or insipidus: too high initial dose or too rapid increase may cause or aggravate symptoms of angina, arrhythmias, myocardial infarction, cardiac failure or a sudden raise in blood pressure.

Children

In congenital hypothyroidism and juvenile myxoedema, the largest dose consistent with freedom from toxic effects should be given. The dosage is guided by clinical response, growth assessment and appropriate thyroid function tests - clinically normal pulse rate and absence of diarrhoea or constipation are the most useful indicators. Thyrotrophin levels may remain elevated during the first year of life in children with neonatal hypothyroidism due to resetting of the hypothalamic-pituitary axis.

For infants with congenital hypothyroidism a suitable starting dose is 25 micrograms levothyroxine sodium, given as 50 micrograms every other day, is advisable. This may be slowly increased by increments of 25 micrograms (given as 50 micrograms on alternate days) every two to four weeks until optimal response is achieved. This dosing regimen is illustrated in **Table 1** above. The same dosing regimen applies to juvenile myxoedema, except that the starting dose for children older than one year may be 2.5 to 5 micrograms/kg/day. The calculated daily dose equivalent should be rounded to the nearest 25 micrograms to determine the actual prescribed dose.

Method of administration

It is recommended that levothyroxine tablets are only prescribed to patients who are able to swallow whole tablets.

Levothyroxine tablets should be taken on an empty stomach, preferably before breakfast.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Thyrotoxicosis.
- Acute myocardial infarction.
- Acute myocarditis.
- Acute pancarditis.

4.4 Special warnings and precautions for use

Adrenal insufficiency

Patients with panhypopituitarism or other causes predisposing to adrenal insufficiency may react unfavourably to levothyroxine treatment, and it is advisable to initiate corticosteroid therapy before giving levothyroxine sodium in these cases.

Cardiac problems

Special care is needed in patients with symptoms of myocardial insufficiency or ECG evidence of myocardial infarction or ischaemia.

Diabetes

Special care is needed in patients with diabetes mellitus or insipidus. Levothyroxine raises blood sugar levels and this may upset the stability of patients receiving antidiabetic agents.

Patients should be monitored carefully to ensure the correct dose is prescribed.

Potential for bone loss

Subclinical hyperthyroidism may be associated with bone loss. In women, long-term levothyroxine sodium therapy has been associated with increased bone resorption, thereby decreasing bone mineral density, especially in post-menopausal women on greater than replacement doses or in women who are receiving suppressive doses of levothyroxine sodium. The increased bone resorption may be associated with increased serum levels and urinary excretion of calcium and phosphorus, elevations in bone alkaline phosphate and suppressed serum parathyroid hormone levels. To minimise the risk of osteoporosis, dosage of levothyroxine should be titrated to the lowest possible effective level.

Elderly

Special care is needed in the elderly.

Paediatric population

Parents of children receiving levothyroxine should be advised that partial loss of hair may occur during the first few months of therapy, but this effect is usually transient and subsequent regrowth usually occurs.

Thyroxine should not be used for the treatment of obesity or weight loss

In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life-threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for anorectic effects.

Malabsorption syndromes

Thyroxine absorption is decreased in patients with malabsorption syndromes. It is advised to treat the malabsorption condition to ensure effective thyroxine treatment with regular thyroxine dose.

Myxoedema

Patients with myxoedema have an increased sensitivity for thyroid hormones; in these patients the starting dose should be low with slow dosing increments.

Pregnancy

During pregnancy, serum thyroxine levels may decrease with a concomitant increase in serum TSH level to values outside the normal range. Patients taking levothyroxine should have their TSH measured during each trimester. An elevated serum TSH level should be corrected by an increase in the dose of levothyroxine. Since postpartum TSH serum levels are similar to preconception values, levothyroxine dosage can be reduced to the pre-pregnancy dose.

4.5 Interaction with other medicines and other forms of interaction

Anticoagulants

Levothyroxine increases the effect of anticoagulants and it may be necessary to reduce the dose of anticoagulant if excessive hypoprothrombinaemia and bleeding are to be avoided.

Phenytoin

Phenytoin levels may be increased by levothyroxine.

Anticonvulsants

Anticonvulsants such as carbamazepine and phenytoin enhance the metabolism of thyroid hormones and may displace them from plasma proteins. Initiation or discontinuation of anticonvulsant therapy may alter levothyroxine sodium dose requirements. Enzyme inducers like rifampicin and barbiturates increase the metabolism and excretion of thyroxine, resulting in increased thyroxine requirements.

Propylthiouracil, glucocorticoids, amiodarone and iodine containing contrast media

Medicines that (partially) inhibit the peripheral transformation of T4 or T3 – like propranolol, amiodarone, lithium, iodine, oral contrast agents, propylthiouracil and glucocorticoids – lower the T3 level and therefore also the therapeutic effect.

Cardiac glycosides

If co-administered with cardiac glycosides, adjustment of dosage of cardiac glycoside may be necessary.

Sympathomimetic agents

The effects of sympathomimetic agents are also enhanced.

Tricyclic antidepressants

Levothyroxine increases receptor sensitivity to catecholamines thus accelerating the response to tricyclic antidepressants.

Cholestyramine

Cholestyramine, calcium-, aluminium-, magnesium-, iron supplements, polystyrene sulfonates, sucralfate, lanthanum, bile acid sequestrants (e.g. colestipol), anion/cation exchange resins (e.g. kayexalate, sevelamer), and proton pump inhibitors concurrently reduces the gastrointestinal absorption of levothyroxine. Separate the dosages of thyroxine and the above-mentioned medicines as much as possible to avoid interaction in the stomach or the small bowel.

Soy supplements

Soy-containing compounds and high-fibre diets can decrease the intestinal absorption of thyroxine. Therefore, a dosage adjustment of thyroxine may be necessary, in particular at the beginning or after termination of nutrition with soy supplements.

Weight loss drugs

Orlistat may decrease levothyroxine absorption which may result in

hypothyroidism. To avoid this orlistat and levothyroxine should be administered at least 4 hours apart. Regular monitoring for changes in thyroid function is required.

Antidiabetics

Thyroxine can increase the need for insulin or oral antidiabetics in patients with diabetes. Lowering the dose of thyroxine can cause hypoglycemia if the insulin or oral antidiabetics dose remains unchanged.

Statins

Reports indicate that some HMG-CoA reductase inhibitors (statins), such as simvastatin and lovastatin, may increase thyroid hormone requirements in patients receiving thyroxine therapy. It is unknown if this occurs with all statins. Close monitoring of thyroid function and appropriate thyroxine dose adjustments may be necessary when thyroxine and statins are co-prescribed.

Decrease of thyroxine dosage requirements

A number of drugs may decrease serum concentration of thyroxine-binding globulin, and therefore decrease thyroxine dosage requirements, including androgens and anabolic steroids.

Anti-inflammatory drugs

False low plasma concentrations have been observed with concurrent anti-inflammatory treatment such as phenylbutazone or acetylsalicylic acid and thyroxine therapy. Administration of acetylsalicylic acid together with thyroxine results in an initial transient increase in serum free T4. Continued administration results in normal free T4 and TSH concentrations, and therefore, patients become clinically euthyroid.

Sertraline

The concurrent use of sertraline can reduce serum levels of thyroxine (with concomitant increased TSH levels).

Increase of thyroxine dosage requirements

- A number of other drugs may decrease absorption of thyroxine sodium, and therefore increase thyroxine dosage requirements. These include antacids (e.g. aluminium hydroxide), bile acid sequestrants (e.g. colestipol), cation exchange resins (e.g. kayexalate), sucralfate, calcium carbonate and ferrous sulphate
- Co-administration of oral contraceptives, as well as a number of other drugs including oestrogen, tamoxifen, clofibrate, methadone and 5-fluorouracil may increase serum concentration of thyroxine-binding globulin, and therefore increase thyroxine dosage requirements
- Treatment with tyrosine kinase inhibitors (e.g. imatinib and sunitinib) was associated with increased thyroxine dosage requirements in hypothyroid patients
- Treatment with amiodarone has been associated with multiple effects on thyroid function including increased thyroxine dosage requirements in hypothyroid patients.

Ritonavir

Post-marketing cases have been reported indicating a potential interaction between ritonavir containing products and levothyroxine. Thyroid-stimulating hormone (TSH)

should be monitored in patients treated with levothyroxine at least the first month after starting and/or ending ritonavir treatment.

Thyroid function tests

A number of drugs may affect thyroid function tests and this should be borne in mind when monitoring a patient on levothyroxine sodium therapy.

4.6 Pregnancy and lactation

Pregnancy

Levothyroxine has been taken by a large number of pregnant women and women of childbearing age without any form of definite disturbances in the reproductive process having been observed so far. Thyroid hypo- or hyperactivity in the mother may, however, unfavourably influence the foetal outcome or well-being.

Breastfeeding

Levothyroxine is excreted in breast milk in low concentrations and this may be sufficient to interfere with neonatal screening for hypothyroidism.

Fertility

No information held by the sponsor.

4.7 Effects on ability to drive and use machines

Levothyroxine is not expected to interfere with the ability to drive or operate machinery based on the pharmacokinetic and pharmacodynamic properties.

4.8 Undesirable effects

The following effects are indicative of excessive dosage and usually disappear on reduction of dosage or withdrawal of treatment for a few days.

Immune system disorders

Hypersensitivity reactions such as skin rash, pruritus and anaphylactic reactions have been reported.

Metabolism and nutrition disorders

Increased appetite, excessive loss of weight.

Gastrointestinal disorders

Abdominal cramps, nausea, vomiting, diarrhoea.

Nervous system disorders

Headache, tremors, seizure. Rare cases of pseudotumour cerebri (benign intracranial hypertension) have been reported especially in children.

Psychiatric disorders

Anxiety, emotional lability, nervousness, excitability, insomnia, restlessness, psychotic depression.

Cardiac disorders

Anginal pain, cardiac arrhythmias, palpitation, tachycardia, increased blood pressure, heart failure, myocardial infarction.

Endocrine disorders

Hyperthyroidism

Respiratory, thoracic and mediastinal disorders

Dyspnoea

Musculoskeletal, connective tissue and bone disorders

Cramps in skeletal muscle, muscular weakness. Excessive dose may result in craniosynostosis in infants and premature closure of epiphyses in children with compromised adult height.

Skin and subcutaneous tissue disorders

Sweating, hair loss.

Vascular disorders

Flushing.

Investigations

Decreased bone mineral density.

Reproductive system and breast disorders

Menstrual irregularity, impaired fertility.

General disorders and administration site conditions

Fatigue, heat intolerance, fever.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions

<https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Symptoms

In addition to exaggeration of side effects the following symptoms may be seen:

Agitation, confusion, irritability, hyperactivity, headache, sweating, mydriasis, tachycardia, arrhythmias, tachypnoea, pyrexia, increased bowel movements and convulsions.

The appearance of clinical hyperthyroidism may be delayed for up to five days.

Thyrotoxic crisis has been occasionally reported following massive or chronic intoxication, leading to cardiac arrhythmias, heart failure and coma.

Treatment

Gastric lavage or emesis is required if the patient is seen within several hours of taking the dose.

Treatment is symptomatic, and tachycardia has been controlled in adults by 40 mg doses of propranolol given every six hours and other symptoms by diazepam and/or chlorpromazine as appropriate.

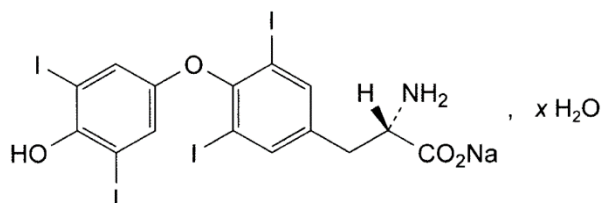
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Thyroid hormones, ATC code: H03AA01

Chemical structure



Sodium (2S)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]propanoate

$C_{15}H_{10}I_4NNaO_4 \cdot xH_2O$ with $x \approx 5$

CAS number: 25416-65-3

Mechanism of action

Levothyroxine sodium is the monosodium salt of the levorotary isomer of thyroxine.

Levothyroxine (T4) is a naturally occurring hormone produced by the thyroid gland and converted to the more active hormone triiodothyronine (T3) in peripheral tissues. The precise signals controlling the conversion of T4 to T3 within the cell are not known. The thyroid hormones are required for normal growth and development, particularly of the nervous system.

They increase the resting or basal metabolic rate of the whole organism and have stimulatory effects on the heart, skeletal muscle, liver and kidney. Thyroid hormones enhance lipolysis and the utilization of carbohydrate.

100 microgram levothyroxine is equivalent in activity to 20 to 30 microgram liothyronine/triiodothyronine or 60 mg Thyroid BP and/or local pharmacopoeia specification.

This medicine has been given a provisional consent under Section 23 of the Act. This means that further evidence on this medicine is awaited or that there are specific conditions of use. Provisional consent is valid until 11 November 2020.

5.2 Pharmacokinetic properties

Absorption

Following oral administration the absorption of levothyroxine is incomplete and variable, especially when taken with food. The amount absorbed increases during fasting conditions.

Levothyroxine is nearly totally bound to serum protein.

Metabolism

The main pathway for the metabolism of levothyroxine (T4) is its conversion, by deiodination, to the active metabolite triiodothyronine (T3). Further deiodination of T4 and T3 leads to production of inactive products.

Elimination

Levothyroxine is eliminated slowly from the body with a half-life of approximately 7 days in a normal person. This may be reduced in hyperthyroid states or increased in hypothyroid patients.

Renal or hepatic diseases do not appear to have any significant effect on the disposition of levothyroxine.

In man, approximately 20 - 40% of levothyroxine is eliminated in the faeces and approximately 30 - 55% of a dose of levothyroxine is excreted in the urine.

5.3 Preclinical safety data

No further data of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Maize starch
Lactose
Acacia powdered
Magnesium stearate
Purified water

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months for Levothyroxine 100 microgram tablets
18 months for Levothyroxine 50 microgram tablets

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

50 microgram tablets in blister packaging with PVC/PVdC film (heat treated foil/heat seal lacquer) containing 28 tablets per pack.

100 microgram tablets in blister packaging with PVC/PVdC film (heat treated foil/heat seal lacquer) containing 28 tablets per pack.

6.6 Special precautions for disposal and other handling

No special requirements

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Boucher & Muir (NZ) Ltd t/a Mercury Pharma (NZ)
39 Anzac Road

Browns Bay
Auckland 0753

Phone 0800 565 633

9 DATE OF FIRST APPROVAL

Date of grant of Provisional Consent to distribute the medicine: 6 November 2008

10 DATE OF REVISION OF THE TEXT

13 September 2019

Summary table of changes:

Section changed	Summary of new information
4.5	Addition of Ritonavir interaction and re-arrangement of existing text in the same section
4.8	Undesirable effect Craniosynostosis has been moved from congenital, familial and genetic disorders to musculoskeletal, connective tissue and bone disorders